

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
2 June 2005 (02.06.2005)

PCT

(10) International Publication Number
WO 2005/049031 A1

(51) International Patent Classification⁷: **A61K 31/498**,
31/513, 31/7068, A61P 35/00

(74) Agent: Marks & Clerk; 66-68 Hills Road, Cambridge,
Cambridgeshire CB2 1LA (GB).

(21) International Application Number:
PCT/GB2004/050026

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AF, AG, AI, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(22) International Filing Date:
15 November 2004 (15.11.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/519,690 13 November 2003 (13.11.2003) US

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GI,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR), OAPI (BF, BJ, CI, CG, CL, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US):
PHARMA MAR, S.A.U. [ES/ES]; Polígono Indus-
trial La Mina, Avda. de los Reyes, 1, Colmenar Viejo,
E-28770 Madrid (ES).

(71) Applicant (for SD only): **RUFFLES, Graham, Keith**
[GB/GB]; 66-68 Hills Road, Cambridge, Cambridgeshire
CB2 1LA (GB).

Published:
— with international search report

(72) Inventor; and

(75) Inventor/Applicant (for US only): **RYBAK, Mary, Ellen**
[US/US]; 3 Stout Road, Princeton, NJ 08540 (US).

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: COMBINATION

(57) Abstract: Methods of treating a human body for cancer are provided. In one aspect, a therapeutic amount of capecitabine is administered in combination with ET-743 in a dose range between 0.75 and 1.4 mg/m² for ET-743. In a related aspect, an effective therapeutic amount of ET-743 is administered in combination with capecitabine in a dose range between 1500 to 2500 mg/m/day for capecitabine.



WO 2005/049031 A1

Combination

The invention relates to a combination of medicaments, more particularly a combination of medicaments for use in the treatment of cancer.

FIELD OF THE INVENTION

The present invention is directed to the use of ecteinascidin 743 in combination with another active drug for the treatment of cancer.

BACKGROUND OF THE INVENTION

Cancer comprises a group of malignant neoplasms that can be divided into two categories, carcinoma, comprising a majority of the cases observed in the clinics, and other less frequent cancers, which include leukemia, lymphoma, central nervous system tumors and sarcoma. Carcinomas have their origin in epithelial tissues while sarcomas develop from connective tissues and those structures that had their origin in mesoderm tissues. Sarcomas can affect, for instance, muscle or bone and occur in the bones, bladder, kidneys, liver, lung, parotid, spleen, etc.

Cancer is invasive and tends to metastasise to new sites. It spreads directly into surrounding tissues and also may be disseminated through the lymphatic and circulatory systems.

Many treatments are available for cancer, including surgery and radiation for localised disease, and drugs. However, the efficacy of available treatments on many cancer types is limited, and new, improved forms of treatment showing clinical benefit are needed.

This is especially true for those patients presenting with advanced and/or metastatic disease. It is also true for patients relapsing with progressive disease after having been previously treated with established therapies for which further treatment with the same therapy is mostly ineffective due to acquisition of resistance or to limitations in administration of the therapies due to associated toxicities.

Chemotherapy plays a significant part in cancer treatment, as it is required for treatment of advanced cancers with distant metastasis and often helpful for tumor reduction before surgery. Many anti-cancer drugs have been developed based on various modes of action.

The most commonly used types of anticancer agents include: DNA-alkylating agents (for example, cyclophosphamide, ifosfamide), antimetabolites (for example, methotrexate, a folate antagonist, and 5-fluorouracil, a pyrimidine antagonist), microtubule disrupters (for example, vincristine, vinblastine, paclitaxel), DNA intercalators (for example, doxorubicin, daunomycin, cisplatin), and hormone therapy (for example, tamoxifen, flutamide). The ideal antineoplastic drug would kill cancer cells selectively, with a wide therapeutic index relative to its toxicity towards non-malignant cells. It would also retain its efficacy against malignant cells, even after prolonged exposure to the drug.

Unfortunately, none of the current chemotherapies possess an ideal profile. Most possess very narrow therapeutic indexes and, in

practically every instance, cancerous cells exposed to slightly sublethal concentrations of a chemotherapeutic agent will develop resistance to such an agent, and quite often cross-resistance to several other antineoplastic agents.

The ecteinascidins (herein abbreviated ETs) are exceedingly potent antitumor agents isolated from the marine tunicate *Ecteinascidia turbinata*. Several ecteinascidins have been reported previously in the patent and scientific literature. See, for example U.S. Pat. No. 5,089,273, which describes novel compounds extracted from the tropical marine invertebrate, *Ecteinascidia turbinata*, and designated therein as ecteinascidins 729, 743, 745, 759A, 759B and 770. These compounds are useful as antibacterial and/or antitumor agents in mammals. U.S. Pat. No. 5,478,932 describes ecteinascidins isolated from the Caribbean tunicate *Ecteinascidia turbinata*, which provide *in vivo* protection against P388 lymphoma, B16 melanoma, M5076 ovarian sarcoma, Lewis lung carcinoma, and the LX-1 human lung and MX-1 human mammary carcinoma xenografts.

One of the ETs, ecteinascidin-743 (ET-743), is a novel tetrahydroisoquinoline alkaloid with considerable antitumor activity in murine and human tumors *in vitro* and *in vivo*, and is presently in clinical trials. ET-743 possesses potent antineoplastic activity against a variety of human tumor xenografts grown in athymic mice, including melanoma and ovarian and breast carcinoma.

A clinical development program of ET-743 in cancer patients was started with phase I studies investigating 1-hour, 3-hour, 24-hour and 72-hour intravenous infusion schedules and a 1 hour daily x 5 (dx5) schedule. Promising responses were observed in patients with sarcoma and breast and ovarian carcinoma. Therefore this new drug is

currently under intense investigation in several phase II clinical trials in cancer patients with a variety of neoplastic diseases. Further detail on the use of ET-743 for the treatment of the human body for cancer is given in WO 0069441, incorporated herein by reference in its entirety.

A recent review of ET-743, its chemistry, mechanism of action and preclinical and clinical development can be found in van Kesteren, Ch. *et al.*, **2003**, *Anti-Cancer Drugs*, 14 (7), pages 487-502: "Yondelis (trabectedin, ET-743): the development of an anticancer agent of marine origin", and references therein.

Combination therapy using drugs with different mechanisms of action is an accepted method of treatment which helps prevent development of resistance by the treated tumor. *In vitro* activity of ET-743 in combination with other anticancer agents has been studied, see for example WO 02 36135, incorporated herein by reference in its entirety.

It is an object of the invention to provide an efficacious combination product for treatment of cancer. More particularly, an object of this invention is an effective cancer combination therapy.

SUMMARY OF THE INVENTION

According to the present invention, we provide a combination therapy for the treatment of cancer which employs ecteinascidin 743 and 5-fluorouracil. Typical dosing protocols for the combination therapy are provided, where the 5-fluorouracil is given in the form of a pro-drug, especially an oral pro-drug exemplified by capecitabine (Xeloda®). From phase I clinical trials, we have determined that a

5

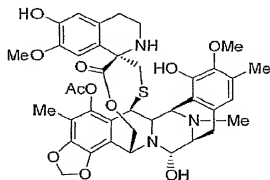
combination of ET-743 and capecitabine is tolerable and feasible, with evidence of antitumor activity.

We also provide a method of treating a cancer patient, which comprises administering ET-743 and a pro-drug of 5-fluorouracil, notably capecitabine. The ET-743 and pro-drug of 5-fluorouracil are preferably administered sequentially, with multiple oral administrations of the pro-drug of 5-fluorouracil following infusion of ET-743.

We further provide the use of ET-743 in the preparation of a medicament for carrying out the method of treatment. We also provide the use of the pro-drug of 5-fluorouracil, notably capecitabine, in the preparation of a medicament for carrying out the method of treatment. We provide the use of ET-743 and the pro-drug of 5-fluorouracil, notably capecitabine, in the preparation of a medicament for carrying out the method of treatment.

DETAILED DESCRIPTION

ET-743 is a natural compound represented by the following formula:



As used herein, the term "ET-743" also covers any pharmaceutically acceptable salt, ester, solvate, hydrate or a prodrug compound which, upon administration to the recipient is capable of providing (directly or indirectly) the compound ET-743. The preparation of salts and other derivatives, and prodrugs, can be carried out by methods known in the art.

ET-743 is typically supplied and stored as a sterile lyophilized product, with ET-743 and excipient in a formulation adequate for therapeutic use, in particular a formulation containing mannitol and a phosphate salt buffered to an adequate pH.

It is currently preferred to administer the ET-743 by infusion. The infusing step is typically repeated on a cyclic basis, which may be repeated as appropriate over for instance 1 to 35 cycles. The cycle includes a phase of infusing ET-743, and usually also a phase of not infusing ET-743. Typically the cycle is worked out in weeks, and thus the cycle normally comprises one or more weeks of an ET-743 infusion phase, and one or more weeks to complete the cycle. In one embodiment a cycle of 3 weeks is preferred, alternatively it can be from 2 to 6 weeks. The infusion phase can itself be a single administration in each cycle of say 1 to 72 hours, more usually of about 1, 3 or 24 hours, or infusion on a daily basis in the infusion phase of the cycle for preferably 1 to 5 hours, especially 1 or 3 hours. Thus, for example, the ET-743 might be administered on each of the first five days of a 3 week cycle. We currently prefer a single administration at the start of each cycle. Preferably the infusion time is about 1, 3 or 24 hour. In one embodiment an infusion time of about 3 hours is preferred.

The dose will be selected according to the dosing schedule, having regard to the existing data on Dose Limiting Toxicity, on which see for

example the incorporated WO patent specifications, and also see van Kesteren, Ch. *et al.*, 2003, Anti-Cancer Drugs, 14 (7), pages 487-502: "Yondelis (trabectedin, ET-743): The development of an anticancer agent of marine origin". This article is incorporated herein in full by specific reference.

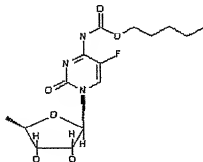
For a single administration of ET-743 at the start of each cycle, we prefer a dose in the range 0.2 to 2 mg/m², more preferably 0.4 to 1.5 mg/m², and most preferably 0.7 to 1.2 mg/m². More generally, for other cycles which involve a single administration at intervals of 1 week or more, the amount of ET-743 is ordinarily in the range 0.7 to 1.2 mg/m². Lower amounts are suitable where there is repeat dosing on a daily schedule.

Most preferably, the ET-743 is given by infusion at a dose of about 0.75 mg/m²- 1.4 mg/m², preferably about 0.9 mg/m²- 1.2 mg/m², most preferably about 0.75 mg/m² or about 0.9 mg/m² on day 1 of a 3 week cycle.

As noted in the incorporated article by van Kesteren, the combination of ET-743 with dexamethasone gives unexpected advantages. It has a role in hepatic prophylaxis. We therefore prefer to administer dexamethasone to the patient, typically at around the time of infusing the ET-743. For example, we prefer to give dexamethasone on the day before ET-743, and/or the day after ET-743. The administration of dexamethasone can be extended, for example to more than one day following ET-743. In particular, we prefer to give dexamethasone at days -1, 2, 3 and 4 relative to a single administration of ET-743 on day 1 of a cycle.

The ET-743 is administered as part of a combination therapy with a pro-drug of 5-fluorouracil, preferably capecitabine.

Capecitabine is of the formula:



Capecitabine is indicated for the treatment of certain cancers. Information is available on the website www.xeloda.com, and the extensive scientific literature on capecitabine. Capecitabine is a pro-drug which is readily absorbed from the gastrointestinal tract. In the liver, a 60 kDa carboxylesterase hydrolyses much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-deoxy-5-fluorouridine (5'-DFUR). The enzyme thymidine phosphorylase (dThdPase) then hydrolyses 5'-DFUR to the active drug 5-fluorouracil (5-FU). Many tissues throughout the body express thymidine phosphorylase. Some human carcinomas express this enzyme in higher concentrations than surrounding normal tissues.

Capecitabine is administered orally as part of the cycle of treating the patient. In the present invention we prefer repeat doses on a daily basis as part of the cycle. We prefer that capecitabine is given for a majority of the days of the cycle, for example for about 2/3, 3/4 or some other fraction of the cycle. For a cycle of 3 weeks, we prefer administration for 14 days, especially days 2 to 15 of a 3 week cycle.

Other administration protocols can be designed having regard to this embodiment. In general, capecitabine is not given on a day when ET-743 is administered, and preferably commencement of administration of capecitabine is on a day after ET-743 administration.

In one embodiment the dosage amount of capecitabine is preferably in the range from 500 to 3000 mg/m²/day, more preferably 1500 to 2500 mg/m²/day, and even most preferably a dose of about 1500 mg/m²/day, about 1600 mg/m²/day or about 2000 mg/m²/day. This dosage can be administered in fractions, for example in a twice-daily regimen.

Most preferably, the capecitabine is given orally at a dose of about 1500 mg/m²/day, about 1600 mg/m²/day or about 2000 mg/m²/day on days 2 to 15 of each cycle.

Other pro-drugs of 5-fluorouracil can be employed in place of capecitabine. Such pro-drugs include other compounds which metabolise to 5'-deoxy-5-fluorouridine, and thence to 5-fluorouracil. For example, reference is made to US 4,996,891 to Fujiu *et al.*, and US 5,472,949 to Arasaki *et al.* The patents are incorporated herein in full by specific reference. In particular, for the present invention, we prefer that the pro-drug is a compound of claim 1 of US 4,966,891 or a compound of claim 1 of US 5,472,949.

Depending on the type of tumor and the developmental stage of the disease, the treatments of the invention are useful in preventing the risk of developing tumors, in promoting tumor regression, in stopping tumor growth and/or in preventing metastasis. In particular, the method of the invention is suited for human patients, especially those who are relapsing or refractory to previous chemotherapy. First line

therapy is also envisaged.

Preferably, the combination therapy is used according to the above schedules and dosages for the treatment of sarcoma, osteosarcoma, ovarian cancer, breast cancer, melanoma, vaginal cancer, gastric cancer, adenocarcinoma, colorectal cancer, mesothelioma, renal cancer, endometrial cancer and lung cancer. Most preferably the patients are breast cancer patients.

In a further aspect of the present invention, a medical kit for administering ET-743 in combination with a pro-drug of 5-fluorouracil is provided, comprising printed instructions for administering ET-743 according to the dosing schedules set forth above, and a supply of ET-743 in dosage units for at least one cycle, wherein each dosage unit contains the appropriate amount of ET-743 for the treatments as defined above and a pharmaceutically acceptable carrier.

Although guidance for the dosage is given above, the correct dosage of the compounds will vary according to the particular formulation, the mode of application, and the particular situs, host and tumor being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

EXAMPLE: Phase I Clinical trial

The objective of this study was to determine the maximum tolerated dose (MTD) of the combination of ET-743 administered over 3

hours intravenously on Day 1 and capecitabine orally administered twice daily on Days 2-15. An additional objective was to evaluate the safety profile of this regimen.

The patients' enrolment to the study was carried out according to the standard inclusion criteria, including creatinine and liver function tests within normal limits and ECOG performance status 0-1. In addition, standard exclusion criteria were also followed including known CNS metastasis and peripheral neuropathy > grade 1.

Dose-limiting toxicity (DLT) was defined as:

- Grade 3-4 non-hematologic toxicity, excluding nausea & vomiting (N/V) in the absence of optimal supportive care, grade 3 transaminitis < 7 days, and hand-foot syndrome.
- Grade 4 neutropenia x 5 days or with fever/sepsis.
- Treatment delay of more than 21 days.
- Platelets < 25,000.

Drug administration was conducted on 21-day cycles. ET-743 was administered as a 3-hour infusion i.v. on day 1 of each cycle (every 3 weeks). Dexamethasone was administered from day -1 to day 3. Capecitabine was orally administered twice-daily on days 2-15 every 3 weeks. In addition, capecitabine was administered at the fixed dose of 2000 mg/m²/day, while ET-743 was started at 400 µg/m² and escalated thereafter in subsequent cohorts of at least 3 new cases.

Table 1 shows the patient characteristics.

Table 1

Number of patients (courses)	14 (50)
Median courses/patient (range)	2 (1-10)

Male:female	5:9
PS 0:1	3:11
Median age (range)	52 (19-70)
Prior chemotherapy (none)	13 (1)
Tumor types	
sarcoma	7
breast, ovarian, cervical, cholangiocarcinoma, gastric, melanoma, vaginal, adenocarcinoma	1 each

Table 2 shows the number of patients exposed in each dose escalation level and the dose limiting toxicities observed.

Table 2

Cohort	ET-743 (mg/m ²)	Capecitabine (mg/m ²)	# Patients	# cycles
1	0.4	2000	3	13
2	0.6	2000	6*	23
3	0.75	2000	3	10
4	0.9	2000	2**	4

*DLT: grade 3 mucositis and febrile neutropenia

**DLT: grade 3 nausea and dehydration

Table 3 shows the frequently reported drug-related hematologic toxicities. In order to define the toxicity grade, NCI common criteria is used.

Table 3

	Grade/Number of Cycles	
	3	4
Neutropenia	2	1

Thrombocytopenia	0	0
Anemia	1	0

(Total courses administered: 50)

Table 4 shows the frequently reported drug-related non-hematologic toxicities. In order to define the toxicity grade, NCI common criteria is used.

Table 4

	Grade/Number of Cycles			
	1	2	3	4
Nausea/Vomiting	25/11	0	4/2	0
Fatigue	15	7	1	0
Transaminitis	29	7	0	0
Hand-Foot Syndrome	10	9	2	0
Diarrhea/Constipation	8/13	1/3	4/0	0
Alk Phos/Bilirubin	11/6	1/5	0	0
Mucositis	4	1	1	0

(Total courses administered: 50)

Regarding the antitumoral activity of the combination, 13 of 14 patients were evaluable for response (1 patient were removed from study for toxicity after 1 cycle). Seven patients (4 sarcoma, 1 each gastric, breast, vaginal, adenocarcinoma) had stable disease after 10, 6, 5, 2, 3, 4, and 3 cycles. One patient with cholangiocarcinoma had a partial response after 8 cycles. Five patients progressed after 1- 2 cycles

Claims

1. A method of treating a human body having cancer comprising administering an effective therapeutic amount of ET-743 in combination with an effective therapeutic amount of 5-fluorouracil or a pro-drug thereof.
2. The method according to claim 1, wherein ET-743 is administered in combination with a 5-fluorouracil pro-drug.
3. The method according to claim 2, wherein ET-743 is administered in combination with capecitabine.
4. The method according to claim 3, wherein capecitabine and ET-743 are provided as separate medicaments for administration at different times.
5. The method according to claim 4, wherein capecitabine is administered in a dose range between 1500 to 2500 mg/m²/day.
6. The method according to claim 4, wherein ET-743 is administered in a dose range between 0.75 and 1.4 mg/m².
7. The method according to claim 5 or 6, wherein capecitabine is administered in a dosage of up to 2000 mg/m²/day and ET-743 is administered in a dosage of up to 1.2 mg/m².

8. The method according to claim 7, wherein capecitabine is administered in a dosage about $1600 \text{ mg/m}^2/\text{day}$ and ET-743 is administered in a dosage about 0.9 mg/m^2 .

9. The method according to claim 5 or 6, wherein capecitabine is orally administered.

10. The method according to claim 9, wherein ET-743 is administered by intravenous injection.

11. The method according to claim 10, wherein the infusion time for intravenous injection of ET-743 is up to 24 hours.

12. The method according to claim 11, wherein the infusion time for intravenous injection of ET-743 is about 3 hours for ET-743.

13. The method according to claim 10, where the infusions of ET-743 are carried out at an interval of 1 to 6 weeks.

14. The method according to claim 13, wherein the infusion of ET-743 is carried out once every 21 days.

15. The method according to claim 14, wherein the infusion of ET-743 is carried out on day 1 and the administration of capecitabine from days 2 to 15, every 21 days.

16. The method according to claim 15, wherein capecitabine is administered twice-daily.

17. A method according to any preceding claim, in which the patient has a cancer selected from sarcoma, osteosarcoma, ovarian cancer, breast cancer, melanoma, vaginal cancer, colorectal cancer, gastric cancer, adenocarcinoma, mesothelioma, renal cancer, endometrial cancer and lung cancer.

18. A method according to claim 17, in which the patient has a cancer selected from sarcoma, breast cancer, gastric cancer, vaginal cancer and adenocarcinoma.

19. The use of ET-743 in the preparation of a medicament for a method according to any of claims 1 to 18.

20. The use of 5-fluorouracil or a pro-drug thereof in the preparation of a medicament for a method according to any of claims 1 to 18.

21. A medical kit for administering ET-743 in combination with capecitabine, comprising a supply of ET-743 in dosage units for at least

one cycle, wherein each dosage unit contains the appropriate amount of ET-743 for the treatments and a pharmaceutically acceptable carrier, and printed instructions for administering ET-743 according to a dosing schedule.

INTERNATIONAL SEARCH REPORT

In: application No
PCT/GB2004/050026

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/498 A61K31/513 A61K31/7068 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPQ-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/69441 A (PHARMA MAR, S.A; BOWMAN, ANGELA; CVITKOVIC, ESTEBAN; DEMETRI, GEORGE,) 23 November 2000 (2000-11-23) cited in the application the whole document page 8, line 19	1-21
X	WO 03/039571 A (PHARMAMAR S.A; JIMENO, JOSE; RUIZ CASADO, ANA; LOPEZ LAZARO, LUIS; ROW) 15 May 2003 (2003-05-15) the whole document page 14, line 29	1-21
	----- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

11 February 2005

Date of mailing of the international search report

23/02/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5618 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Economou, D

INTERNATIONAL SEARCH REPORT

 Int. application No
 PCT/GB2004/050026

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/36135 A (PHARMA MAR, S.A; TAKAHASHI, NAOTO; WEITMAN, STEVE; D'INCALCI, MAURIZIO) 10 May 2002 (2002-05-10) cited in the application the whole document page 1, line 18 -----	1-21
X	US 5 472 949 A (ARASAKI ET AL) 5 December 1995 (1995-12-05) cited in the application the whole document column 3, line 11 -----	1-21
X	NAOTO TAKAHASHI ET AL.: "Sequence-dependent Synergistic Cytotoxicity of Ecteinascidin-743 and Paclitaxel in Human Breast Cancer Cell Lines in Vitro and in Vivo" CANCER RESEARCH, vol. 62, no. 23, 1 December 2002 (2002-12-01), pages 6909-6915, XP002317292 US abstract page 6912, right-hand column, line 40 - line 49 -----	1-21

INTERNATIONAL SEARCH REPORT

 Int. application No
 PCT/GB2004/050026

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0069441	A	23-11-2000	AU 777417 B2 14-10-2004
			AU 4597500 A 05-12-2000
			BG 106171 A 28-06-2002
			BR 0010531 A 04-06-2002
			CA 2373794 A1 23-11-2000
			CN 1360503 T 24-07-2002
			CZ 20014081 A3 13-11-2002
			EP 1176964 A1 06-02-2002
			WO 0069441 A1 23-11-2000
			HU 0201187 A2 28-09-2002
			JP 2002544231 T 24-12-2002
			MX PA01011562 A 30-07-2002
			NO 20015516 A 11-01-2002
			NZ 515423 A 30-04-2004
			PL 352931 A1 22-09-2003
			SK 16442001 A3 05-03-2002
			TR 200103819 T2 22-04-2002
			NZ 529801 A 19-12-2003
WO 03039571	A	15-05-2003	BR 0213424 A 14-12-2004
			CA 2462502 A1 15-05-2003
			EP 1435988 A1 14-07-2004
			WO 03039571 A1 15-05-2003
			US 2005004018 A1 06-01-2005
WO 0236135	A	10-05-2002	AU 1249902 A 15-05-2002
			BG 107843 A 30-06-2004
			BR 0115162 A 21-10-2003
			CA 2428160 A1 10-05-2002
			CN 1486193 T 31-03-2004
			CZ 20031327 A3 12-11-2003
			EP 1365808 A2 03-12-2003
			WO 0236135 A2 10-05-2002
			HU 0400648 A2 28-06-2004
			JP 2004517056 T 10-06-2004
			NO 20032027 A 04-07-2003
			NZ 525730 A 24-12-2004
			PL 361389 A1 04-10-2004
			SK 5492003 A3 02-03-2004
			US 2004108086 A1 10-06-2004
			ZA 200303474 A 06-08-2004
US 5472949	A	05-12-1995	AT 137244 T 15-05-1996
			AU 671491 B2 29-08-1996
			AU 5069093 A 30-06-1994
			BG 61485 B1 30-09-1997
			BG 98304 A 03-01-1995
			BR 9305089 A 05-07-1994
			CA 2103324 A1 19-06-1994
			CN 1094056 A ,C 26-10-1994
			CZ 9302731 A3 13-07-1994
			DE 69302360 D1 30-05-1996
			DE 69302360 T2 31-10-1996
			DK 602454 T3 29-07-1996
			EE 3086 B1 15-04-1993
			EP 0602454 A1 22-06-1994
			ES 2086856 T3 01-07-1996
			FI 935616 A 19-06-1994

INTERNATIONAL SEARCH REPORT

Int .pplication No
PCT/GB2004/050026

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5472949 A		GR 3020286 T3	30-09-1996
		HK 1005875 A1	29-01-1999
		HR 931430 A1	30-06-1998
		HU 65757 A2	28-07-1994
		HU 9500255 A3	28-09-1995
		JP 2501297 B2	29-05-1996
		JP 6211891 A	02-08-1994
		LT 1627 A , B	15-07-1994
		LV 10625 A	20-04-1995
		LV 10625 B	20-04-1996
		NO 934671 A	20-06-1994
		NZ 250414 A	21-12-1995
		PH 30168 A	21-01-1997
		PL 301541 A1	27-06-1994
		RO 112619 B	28-11-1997
		RU 2135511 C1	27-08-1999
		SI 9300648 A , B	30-09-1994
		SK 144493 A3	05-10-1994
		ZA 9309293 A	18-06-1994